ARE MULTILATERAL MALARIA RESEARCH AND CONTROL PROGRAMS THE MOST SUCCESSFUL? LESSONS FROM THE PAST 100 YEARS IN AFRICA

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Abstract. Multilateral malaria research and control programs in Africa have regained prominence recently as bilateral assistance has diminished. The transnational nature of the threat and the need for inspired leadership, good coordination, and new discoveries to decrease the impact of the disease has led to the founding of the Multilateral Initiative on Malaria, the Roll Back Malaria Project, Global Fund for HIV, Tuberculosis and Malaria (Global Fund), the Medicines for Malaria Venture, and the Malaria Vaccine Initiative, among other groups. Historically, the most striking feature of malaria control and elimination activities was the connectedness and balance between malaria research and control especially, from 1892 to 1949. A combination of scientific originality, perseverance in research, integrated approaches, and social concern were the keys for success. The elimination of *Anopheles gambiae* from Upper Egypt in 1942 using integrated vector control methods is a prime example of malaria control during the first half of the 20th century where those factors were brought together. After 1949, there were three decades of great optimism. Four notable landmarks characterized this period: the Kampala Conference in 1950; the Global Malaria Eradication Program beginning in 1955; the primary health care strategies adopted by most African States after attaining their political independence in the 1960s, and accelerating in the 1980s; and creation of the Special Program in Training and Research in Tropical Diseases at the World Health Organization in 1975. The initial highly encouraging operational results, largely obtained in temperate or subtropical areas where transmission was unstable, engendered undue expectations for the success of identical antimalarial measures elsewhere. Many were convinced that the eradication was in sight, such that support for malaria research virtually ceased. Young, bright scientists were discouraged from seeking a career in a discipline that appeared to soon become superfluous. It took more than three decades to modify antimalarial strategies and to rehabilitate long-term control as an intermediate objective. In Africa, although multilateral malaria programs have grown over the past half century and proved the most successful, fragmentation of co-ordination remains and is a major challenge. The proliferation of malaria programs in the late 1990s has brought substantial additional funds and expertise. However, excessive funding competition and failure of different programs to collaborate has resulted in poor communication and duplication of activities. The capacities of the African nations to conduct high-quality research and to coordinate control efforts are in great jeopardy. There is an urgent need for a non-partisan umbrella organ to coordinate and facilitate the network of alliances and programs in malaria research and control in Africa.

INTRODUCTION

Multilateral programs are those activities involving two or more nations that are channeled through an international or regional agency.[1–3] The definition also includes arrangements where several governments and agencies such a private foundations join efforts in funding or implementing malaria control, training or research program.* We define a regional organization as one involving research or control programs covering more than one country in a specific geographic area.

For malaria, the first large-scale multilateral initiative was the World Health Organization (WHO) Malaria Eradication Program (1955–1969).[4] This global effort, which aimed to eradicate malaria in every part of the world by vector control, achieved regional eradication of the disease in southern Europe and some countries of north Africa and the Middle East. In India and Sri Lanka, malaria was greatly reduced but later rebounded dramatically.[5] Sub-Saharan Africa was excluded from the Malaria Eradication Program, having been declared "not ready" by international experts.[6]

While the WHO Malaria Eradication Program did not succeed, unilateral (one country on its own) and bilateral (i.e., country-to-country) approaches have, with few exceptions, achieved even less success in developing sustainable large-scale research and control activities. The WHO-sponsored† bilateral vector control projects in Cameroon, Nigeria, and Kenya in Africa in the 1960s were largely ineffective on the national scale.[7] During the 1980s and 1990s, malaria control programs in Africa, mainly supported, coordinated, and implemented unilaterally at the country, provincial, and district levels, fell into disrepair or were abandoned entirely.[6] The primary health care movement was supposed to assure prompt, effective patient management to decrease mortality, but this too was ineffective. Problems were compounded by growing resistance of malaria parasites to drugs and anopheline mosquitoes to insecticides, general weaknesses in the

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* This definition is consistent with the United Nations Statistical Database Division that defines multilateral agencies as including but not limited to the Commission of the European Communities and European Development Bank, World Bank, International Finance Corporation, International Development Authority, African Development Bank, African Development Fund, Asian Development Bank, Caribbean Development Bank, International Fund for Agricultural Development, International Money Fund, European Resettlement Fund, Arab Bank for Economic Development in Africa, Arab Fund for Economic and Social Development, Islamic Development Bank, Organization of the Petroleum Exporting Countries Fund for International Development, and United Nations Technical Assistance (United Nations agencies).

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† Confusion exists between multilateral and multi-country programs. Some projects that are defined as unilateral in the literature are also stated to be WHO sponsored. In this report, any arrangement between a United Nations agency and an individual country is defined as bilateral. Investigators were aware that there may be some complexity at the country level where some programs may often be under a multilateral umbrella, but bilateral donors may often have their own programs within the larger program. Multilateral and bilateral are not necessarily mutually exclusive in this case.

health care infrastructure, and economic shocks, which reduced government spending on health care. The malaria situation worsened, and fatalism and resignation towards the disease became widespread.[8]

Due to failure of malaria control working only through the primary health care systems, and the need for improved and new anti-malaria interventions, regional research and control initiatives in Africa, as well as international private and public partnerships, have gained prominence. Examples of these programs include the Multilateral Initiative on Malaria (MIM),[9] the Roll Back Malaria (RBM) Partnership,[10] the Global Fund for HIV, Tuberculosis and Malaria (Global Fund),[11] the Medicines for Malaria Venture (MMV),[12] and the Malaria Vaccine Initiative (MVI).[13] These programs have gained prominence due to their great potential for facilitating important discoveries and coordination of large-scale control actions, which cannot be achieved by a single African country working alone.

There is a growing realization among the African leadership, international development authorities, and the general public of the transnational nature of the threat posed by malaria. In 1992, the Ministerial Conference on Malaria in Amsterdam enunciated a Global Malaria Control Strategy, which was endorsed by The Economic and Social Council of the United Nations in 1994.[14] The World Health Assembly passed a resolution on controlling malaria in Africa in May 1996, and the Organization of African Unity made declarations on malaria in Harare, Zimbabwe in 1997 and in Ouagadougou, Burkina Faso in 1998.[15] In 1996, the African Regional Office of the WHO became increasingly attentive to malaria and launched the African Initiative for Malaria Control (AIM).[16] AIM contributed $9 million in 1997 and 1998 for accelerated implementation of malaria control activities in 10 countries in the region, and provided the foundation for the eventual launch of Roll Back Malaria in 1998. In 1997, the MIM Malaria was established by African and northern country partners with focus on strengthening research capacity in Africa.[9] The heads of African States conference was held in April 2000 in Abuja, Nigeria, which declared the goal of reducing malaria deaths by half by the year 2010.[17] The diverse array of meetings, programs, and activities are testimony to the growing recognition of the regional and global nature of the threat posed by malaria, the complex nature of the actions required, and the need for coordination, and cooperation to address it. While political will and advocacy are important, meetings and resolutions alone do not translate directly into better disease control or discoveries through research. Well-supported, hard work in the field, at the bench, and bedside is required.

The importance of having research and control initiatives working closely has been a recent focus of multilateral programs. While a consensus on the optimal strategy to form the interface between research and control is emerging, scientists and control specialists agree that a multilateral approach needs to be reinvented. Table 1 outlines some advantages and disadvantages of multilateral, bilateral, and unilateral programs.

In the past, only governments, United Nation's organizations, and a few international foundations invested in scientific research and public health in African countries. Private foundations (such as the Rockefeller Foundation) have had a limited focus in the region; the situation is now changing. The private sector and non-governmental organizations (NGOs) are increasing their role.[18,19] Resources from the new philanthropies, such as the Bill and Melinda Gates Foundation, and the wide array of partnership-based initiatives throughout the United Nations system are flowing into malaria research.[20] The partnerships between private and public institutions have been translated into the programs such as MVI and MMV with investments exceeding US$100 million from 1993 to 2003. At the global level, the best example of a multilateral program that has stood the test of time is the Special Program for Research and Training in Tropical Diseases (TDR), an independent global program of scientific collaboration, established in 1975 and co-sponsored by the United Nations Development Program, the World Bank, and the WHO.[21] The model that is emerging is one of scientific collaborations that are "network-based" (a group of institutions working together for a common cause) rather than single "agency-based." This approach is greatly energizing the international alliances.[16,22]

With the gradual growth of the number of trained African leaders to coordinate research and control, the chances for these programs to succeed are now greater than ever.[23] There is a sense of optimism, tempered by the variably fragile demographic transition, urbanization, aging and migration, changing epidemiology of malaria, and increasing intensity and spread of *Plasmodium falciparum* resistance to antimalarials and the *Anopheles* mosquitoes to insecticides.[8,24–26] If the lessons learned over the past 100 years are carefully applied, further gains are assured towards controlling malaria in Africa. This report reviews the history of multilateral malaria research and control programs in Africa with the aim of searching for lessons for informing the new multilateralism

TABLE 1
Comparison of multilateral, bilateral, and unilateral programs for malaria research and control

Factor	Multilateral	Bilateral	Unilateral
Global Coordination/communication	Highly successful	Limited	Low
Leadership (decision making)	Can be ambiguous	Often donor-driven	Decisive
Mutual benefits	High	Varies	Minimal
Partners	Multiple	Two	None
Resources	High	Medium	Low, varies
Sharing experience	Highly successful	Varies	Varies
Standardized methods	High	Varies	Varies
Sustainability	Good	Varies	Fragile
Synergies/network formation	Highly successful	Limited	Low
Time to form coalition	Long	Often long	Short

spirit and underscoring the necessity of linking research and control closely using specific examples.

METHODS

Three distinct periods in the history of malaria research and control programs in Africa are examined. Data comes from a computerized literature search of databases performed with the assistance of the U.S. National Library of Medicine (NLM) and unpublished reports collected by the MIM Secretariat. The search used a grouping of terms encompassing malaria control programs, multilateral activities in malaria, malaria research, and history of malaria in Africa. The search identified 91 articles, of which 61 had relevant information. The articles were classified by year: 1880–1959, 1950–1979, and 1980–2003.

Due to the historical nature of materials reviewed, this report does not purport to conclude definitively which type of program is more successful. The comments on successes or failures are based on judgments made in the literature. Some judgments are without clear justification, and may be misleading. Thus, judgments of program success are not made unless criteria and evidence for were explicit.

1880–1949: ERA OF INGENUITY AND DISCOVERY

Major highlights of the 1880s to the 1940s period were the discovery of the malaria parasite by Laveran in 1880 and the description of the sporogenic cycle of the human malaria parasite in the mosquito by Grassi, Marchiafana, Celli, Bastianelli, Bignami and Ross.[27] In 1874, dichloro-diphenyl-trichloroethane (DDT) was isolated and in 1939 Paul Muller discovered its residual insecticidal properties.

The most striking feature of this period was the connectedness and balance between malaria research and control. The same people who were active in research were also directing the control efforts. Ronald Ross, the scientist who discovered the malaria parasite in wild-caught mosquitoes in Sierra Leone in 1897, was also a public health administrator. Ross's main interest was sanitation and human health.[28] His scientific approach changed after the discovery of the malaria transmission cycle, but his general strategy remained the same: to eliminate the factors indispensable to the multiplication and diffusion of the parasite.[29] Knowledge of the malaria transmission cycle made it possible to define the exact conditions responsible for the propagation of the disease and its persistence in the endemic areas. A similar approach was taken by Grassi in Italy. Epidemiologic research focused on clarifying the conditions that facilitated or prevented the malaria infection carried by the *Anopheles*.[30] The approach of Ross and Grassi linking research to control led to numerous malaria control activities in southern Europe and the first malaria control effort in Africa; quinine, discovered in 1620s in Peru as an effective fever treatment, and larviciding were for the first time used for malaria control in the British army barracks in Freetown, Sierra Leone.[31] The dual research and control roles of the malariologist disappeared at the beginning of 20th century. Regrettably, there have been growing and clearly marked differences and a widening separation between the "scientist" and "control staff." This division has resulted in poor coordination and limited severely the impact of efforts to control and eradicate malaria.[28]

Totally missing from 1880 to 1949 were research or control programs in Africa that involved several nations working together. The few programs that existed were unilateral, fragmented, and undertaken by colonial governments focusing on their territories and workforce. A few programs addressed the malaria problem for multinational mining and shipping companies and covered more than one country. These included the Anglo-American mining company in Zambia (formerly Northern Rhodesia) and South Africa. The strategy combined mass prophylaxis with quinine and landscape engineering, with the aim of limiting stagnant water collections in town centers and mining areas.

Some colonial governments devoted significant resources to research and control of malaria; by 1949, Britain had spent approximately one million pounds (US$1 billion in current dollars) in its colonial territories.[32] This investment yielded varying results; in Mauritius, malaria transmission was halted, but not in the saline swamps of Lagos; a study conducted in Apapa in 1942 concluded that "Lagos, the capital of Nigeria and its main port has presented a special (control) problem."[32] Despite difficulties, there was an emerging change of attitude from fatalism and resignation to consideration of malaria control as attainable. The discovery of the cycle of malaria transmission and the possibility of interrupting it by decreasing contact between people and the *Anopheles* mosquito was a powerful impetus to this change of attitude.[30] However, scientifically based strategies and infrastructure to control malaria were not in place in Africa. Table 2 summarizes key malaria projects linking research and control from 1880 to 1949.

TABLE 2
Malaria research and control in Africa from 1892 to 1949

Initiative	Focus	Duration	Landmarks	Lessons learned
Malaria research and control, Sierra Leone[31]	Research and control in Freetown	1892–1945	Transmission cycle revealed: discovery of human malaria parasites in wild-caught mosquitoes First control program in Africa (Freetown) Establishment of field laboratory	Fragmented, unsustainable control measures; minimal long-term impact on human infection and transmission; local participation; results used promptly
Malaria control in Zambia (ex-Northern Rhodesia)[72]	Control in and around the copper mines	1930–1950	Extensive environmental modification Larviciding Patient treatment and individual protection by house screening	Incidence reduced by 95% within five years; highly effective control

TABLE 3
Multilateral activities from 1950 to 1979 (selected examples in Africa)*

Initiative	Focus	Duration	Landmarks	Lessons learned
Nile Valley (Egypt) Eradication Program[72]	Research and control of invasion of Anopheles gambiae	1942–1969	Larviciding and pyrethrum spraying Research on vectors	Eradication of Anopheles gambiae in upper southern Egypt
Malaria Research and Control Program in east Africa and Kampala Conference, 1950[33]	Research and control Pare-Taveta Scheme	1954–1959	Research on malariometric measures prior to in-door residual spraying with DDT	Infant mortality rates and overall death rates reduced by 50%; transmission negligible, but not stopped
Garki Project, northern Nigeria and Kisumu, western Kenya	Research on the epidemiology and control of malaria in the Sudan Savanah of west Africa	1971–1980	Malaria brought under control in Kisumu but could not be achieved in Garki	Effective control requires strategies tailored for specific setting
WHO-PHC and TDR Programs[21,73]	Research and training, control	1975–	UNDP-World Bank, WHO and Rockefeller Foundation support research and training program, prompt treatment to decrease mortality becomes the main WHO strategy	TDR-attracted research funds and supported a cadre of trained scientists in the tropics

* WHO = World Health Organization; PHC = Primary Health Care; TDR = Special Program for Research and Training in Tropical Diseases; UNDP = United Nations Development Program.

1950–1979: ERA OF OPTIMISM AND HOPE

Optimism for malaria eradication characterized the 1950s to the 1970s. This was followed by a more somber period beginning in 1980, and is marked by proliferation of multilateral activities directed to coordination and integration of efforts. There are four notable landmarks in this period: the Kampala Conference in 1950, the Global Malaria Eradication Program that started in 1955, political independence of most African States in the 1960s, and the creation of the TDR in 1975 (Table 3).

The Kampala Conference in 1950, the first of the multilateral gatherings on malaria in tropical Africa, aimed to take advantage of the impressive results of DDT spraying in other parts of the world to start a malaria control program with the help of governments administering of the African territories.[33] The conference was organized by the WHO to bring together eminent malariologists and other experienced field researchers to work on technical aspects of action plans for malaria control in rural Africa. The main conference recommendation was that malaria in sub-Sahara Africa should be "controlled–by modern methods as soon as feasible, whatever original degree of endemicity and without waiting the outcome of further experiment."[33] However, at the launch of the 1955 global malaria eradication program five years after the Kampala Conference, Africa was not included because intra-domiciliary insecticide spraying was not considered feasible in much of Africa. Exclusion of the most intensely malarious area of the world from the global malaria eradication program is paradoxical because one would have expected such an ambitious undertaking to include areas where the burden was the highest.[6]

Attainment of independence of most African states from the beginning of the 1960s brought optimism for development of control programs at the country level. For some experts, it was imperative that malaria became a priority area for the newly independent states. Fred Soper, head of the Pan American Health Organization, wrote about his trip to Africa in 1959; "Everywhere we went in west Africa there was a more acute sense of impending change. . . . It is obvious that to those who are familiar with malaria in tropical areas particularly in Africa that the proper utilization of technical assistance funds in all fields–agriculture, education, industry, transportation and in other fields, is dependent upon the control of malaria."[34] Because Anopheles gambiae and An. funestus were and are such tremendous widespread vectors of malaria, Soper considered it imperative that malaria programs in Africa "should begin by covering a very large area and must be ready to expand at the periphery even beyond national boundaries if they are to succeed and permanently protect the population concerned."[34] By the late 1960s and early 1970s, regional co-corporation in malaria control became impossible due to political problems and civil unrest including the outbreak of internal conflicts in Nigeria and the Biafran civil war, the overthrow of civilian governments by military dictators in Ghana, Nigeria, Uganda, the Democratic Republic of Congo (Zaire), Somalia, and Ethiopia, and wars for independence in Mozambique, Zimbabwe, Angola, Guinea-Bissau, and Namibia. These conflicts did not allow creation of large-scale regional malaria control programs as envisaged by the experts in the late 1950s; the environment was too chaotic.[35]

Beyond the political problems common in Africa during past four decades, there were four other issues that remained unresolved: the roles of ministries of health; reluctance to confront clearly the need for economical benefits, and technical limitation of eradicating malaria from Africa; limited feasibility of creating a sustainable surveillance system; and the need for better and more appropriate interventions.

Malaria experts often believed that programs should be planned without the involvement of the ministry of health and advice given to "insist on national programs planned in such a way that there should be no interference from the minister of health."[36] Mistrust between international malaria experts and local ministries was so profound that at the WHO regional meeting in Brazzaville in 1959 a request was made for

"independence of action and financing in Liberia where an extensive demonstration national eradication program was to be established covering the entire country. The expectation was that once this had been done arrangements could be made for continuing expansion until the entire area from Mauritania and Senegal to Nigeria had been covered."[34]

The second issue was lack of consensus of the importance of malaria vis-a-vis other problems of public health importance in Africa.[33,37] At the 1959 WHO meeting in Brazzaville, the old question was raised once again, "whether, with all the health problems which exist in Africa, it is justifiable to concentrate large amounts of money and numerous personnel on a single disease especially when it can not be clearly shown that this single disease is the most important health problem or even that the disease is an important cause of death."[34] However, a far greater number of experts at this meeting were convinced that the attack on malaria through vertical programs would set a positive precedent to attack other diseases of animals and plants.[36]

The third issue was the feasibility of having a reliable surveillance system in Africa. The key contention was admission that the attempt to find and treat all parasite carriers, the traditional WHO strategy, would be a most difficult if not impossible undertaking. In 1959, surveillance was recognized as a search for places where transmission was continuing rather than a search for all the individual cases.[34]

The fourth unresolved issue was a choice of interventions to interrupt transmission. While use of residual insecticide was not the cheapest and most efficient way of eradicating malaria in Africa, especially in desert and semi-arid areas, the experience from Brazil showed that a complete elimination of the malaria-transmitting mosquito species had been possible in a three-week period when all potential breeding sites were dusted with Paris green.[34] The 1959 WHO report reflects the controversies around the use of vector control versus drugs: "in spite of its many disadvantages, for example the irritant effect, and lower initial toxicity to *Anopheles,* DDT continues to give excellent results when properly applied. The use of drugs in the malaria programs in Africa region has been on the whole disappointing largely due to the fact that a total coverage of the population with drugs has not been achieved . . . such conditions cannot be obtained and drugs should be reserved for areas where it has been conclusively shown that residual spraying with total coverage cannot interrupt transmission by itself.[34,36]

The optimism tied to the global eradication program resulted in a very large increase in spending on malaria from the mid 1950s to the early 1970s, which was never seen before in the history medicine and public health. The United States contributed nearly a billion dollars, mainly in bilateral assistance.[38] This was the first multilateral effort of its kind, and accounted for more than one-third of total expenditures of the WHO, and the 500-person WHO malaria staff dwarfed all other programs.[39–41] The WHO spent approximately US$70 million from 1972 to 1975 on eradication, even while the program was dying out. In current dollars, this is almost double the RBM program's annual budget of US$35 million.[6,36]

The global malaria program included most countries in Asia and the Americas, but excluded some of the most malarious areas such as tropical Africa, Papua New Guinea, and some of the islands of Indonesia, e.g., Kalimantan, Sulawesi

and West Irian Jaya, because of overwhelming administrative, technical, financial, social, and ecologic difficulties. At the height of the program in the 1960s, the WHO supported limited efforts in Ethiopia, South Africa, and Zimbabwe where elimination was thought feasible because of the conducive health infrastructure and epidemiologic conditions.[42] Only a few urban centers were protected by residual insecticide spraying or larviciding elsewhere in sub-Saharan Africa. Antimalarial activities were restricted to hospitals and dispensaries and antimalarial drugs were available in the open market. A few drug prophylaxis projects using chloroquine, pyrimethamine, or proguanil were initiated in Papua New Guinea, West Irian Jaya, Madagascar, Nigeria, Senegal, and Tanzania through maternal and child health centers, dispensaries, or schools. These activities saved some children, but may have promoted the development of drug resistance in Papua New Guinea, Madagascar, and Tanzania.[4]

The WHO-sponsored research evaluating control methods, with a strong focus on epidemiology and entomology, was conducted in Kisumu, Kenya, and Garki, Nigeria, from 1971 to 1980. These projects looked at what could be achieved with adequate financial and technical assistance.[43,44] It was shown that residual insecticides could achieve interruption of transmission in parts of Kisumu, but not in Garki, even when accompanied by the administration of suppressive antimalaria drugs every two weeks covering more than 90% of the population at each round. A mathematical model that could be used for planning malaria control campaigns in Africa was developed, but was never used by governments in Africa because there were no resources and infrastructure for control activities.

The ultimate failure of the WHO Malaria Eradication Program engendered a general sense of disappointment globally. Despite many disappointments, there was one positive development, the creation of the TDR in 1975. This program has expanded its portfolio and greatly influenced global efforts to combat the major tropical infectious diseases of the poor and disadvantaged. The TDR has had two main objectives: 1) to promote research and generate critical new information, and 2) to strengthen the capacity of low-income endemic countries to undertake research required for developing and implementing these new and improved disease control approaches. The TDR now focuses on 10 infectious diseases: African trypanosomiasis, dengue, leishmaniasis, malaria, schistosomiasis, tuberculosis, Chagas disease (American tryponosomiasis), leprosy, lymphatic filariasis, and onchocerciasis.[21]

1980–2003: PROLIFERATION OF MULTILATERAL ACTIVITIES

For Africa, this period has been characterized by high birth rates, high incidence of communicable diseases (including the devastating advent of human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS]), increasing prevalence of chronic diseases, major climate-related disasters such as droughts and floods, recurrent epidemics (Ebola, meningitis, yellow fever) and, above all, a drastic increase in civil strive resulting in an unprecedented number of refugees and displaced persons.[8] For the first time, a new dimension was added to the malaria conundrum, that of the

disease as a complex emergency. The United Nations defines complex emergency as a "humanitarian crisis in a country, region or society where there is total or considerable breakdown of authority resulting from internal or external conflict and which requires an international response that goes beyond the mandate or capacity of any single agency or the ongoing United Nations country program."[45]

With the recent resurgence of malaria, many multilateral activities emerged in the 1980s and 1990s, underscoring the need for well-coordinated efforts to tackle funding, research coordination, and promotion of private and public sector cooperation.[46,47] Each effort has its unique mission (e.g., research, drug or vaccine development, control, communication, and advocacy, etc). Table 4 summarizes some of the major initiatives of 1990s, their mission, objectives, and coverage. As these organizations and initiatives continued to grow, so did the need for co-ordination and communication. Beyond the programs shown in Table 4, the 1990s saw myriad smaller-scale multilateral programs covering a broad array of research, training, control, and advocacy activities. Figure 1 shows existing and potential linkages between these potentially synergistic programs.

Four of these programs (MIM, the RBM Project, the MMV, and the Global Fund for HIV, Tuberculosis and Malaria) merit special attention due to their potential to have a great effect on malaria research and control over the next decade.

Multilateral Initiative on Malaria. Launched in 1997, this international effort aims to train scientists, coordinate research funding and promote greater research and control leadership in Africa.[48–51] Scientists, funding agencies, governments, pharmaceutical companies, and other members of public and private sectors are involved. The MIM provides training and research grants through a peer-reviewed competitive process, with a budget of approximately $2 million per year.[52] Many of the research programs initiated in 1999 by MIM, managed and administered by WHO/TDR, have developed into regional scientific networks comprising several country teams and scientists. Table 5 shows the regions and countries represented in the networks that address antimalaria drug resistance; epidemiology and information technology; pathogenesis and immunology; and vector biology and insecticide resistance.

In October 2002, an external panel reviewed the progress of the MIM during its first five years and concluded that the original objectives have been realized; "south to south" scientific institutional collaborations have been greatly enhanced, and the MIM Pan-African Malaria Conferences held every three years have provided a vibrant open forum for African scientists and public health workers to network and interact.[53] The inventory of African malaria research centers performed by the first MIM Secretariat has encouraged better use of existing resources and identified areas of need. The successful creation of the rotating MIM Secretariat (Wellcome Trust, United Kingdom, 1997–1999; Fogarty International Center, National Institutes of Health, Bethesda, MD; 1999–2003; and Stockholm University/Karolinska Institute, Stockholm, Sweden, 2003) has provided the malaria community with a reliable, resourceful, and promptly responsive coordinating center.[53]

Roll Back Malaria. Launched in 1998 by the WHO, the World Bank, the United Nations Children's Fund, the United Nations Development Program, and other partners, RBM aims to cut the malaria burden in half by 2010 by advocating and promoting treatment and prevention strategies that include distribution of insecticide-treated bed nets to all pregnant women and children in sub-Saharan Africa.[10,42,54–57] The RBM is not a financing mechanism. It works by encouraging others to dedicate resources to malaria control, to strengthen health systems, and to use a variety of tools through existing networks and partnerships; its budget was $24 million in 2002.[42] Progress is slow but substantial, particularly in surveillance promotion of insecticide-treated bed nets and closer linkage of research to control. One major problem is the frequent change of the RBM leadership since its inception.

Medicines for Malaria Venture. This novel public-private venture was initiated in 1998 by the WHO, the World Bank, and several drug companies.[12,58–60] The goal is to develop at least one new anti-malarial drug or drug combination every five years and make them available to low-income countries. Seven drug discovery projects and five development projects now are in progress, making MMV the largest anti-malarial drug pipeline since World War II. Its budget was $15 million in 2002, with a goal of $30 million per year. Since 2001, the program has received $5 million per year from the Bill and Melinda Gates Foundation.[42]

Global Fund to Fight AIDS, Tuberculosis and Malaria. Launched in 2002, the fund was created to attract, manage, and disburse financial resources through a public-private partnership to reduce the impact of HIV/AIDS, tuberculosis, and malaria, and to contribute to poverty reduction.[11,61,62] The 2003 budget was $1.2 billion and $72 million in multiyear grants for malaria control were approved in April 2002.[42]

1980–2003: MALARIA AND COMPLEX EMERGENCIES

The resurgence of major malaria epidemics in settings with complex emergencies (e.g., refugee camps and areas with civil strife) calls for a different research and control approach than for areas with stable transmission. Morbidity and mortality from malaria in such circumstances contribute substantially to the overall yearly malaria burden. Complex emergencies increase the involvement of NGOs; during strife, governments cannot always provide curative or preventive health care.[6] A major challenge with involvement of NGOs has been that their humanitarian-focused policies and actions are often in conflict with those of the governments. In Burundi, where malaria resistance to chloroquine and sulfadoxime pyrimethamine were prevalent, the national policy recommending the use of ineffective chloroquine and sulfadoxime-pyrimethamine was in conflict with policies of NGOs attempting to achieve short-term malaria control goals.[6]

DISCUSSION

There have been few historical reviews of multilateral efforts dealing with malaria during the past 100 years. Profound changes have occurred, not only in the prevalence and impact of malaria throughout the world, but in development of ways the disease can best be controlled.[4]

TABLE 4
Major malaria initiatives of the 1990s and 2000s*

Name	Year began	Mission, objective, budget, and website	Location of secretariat	Coverage
The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund)	2002	Attract, manage, and disburse financial resources through a new public-private partnership to reduce the impact of HIV/AIDS, tuberculosis, and malaria and contribute to poverty reduction. Total budget: $1.2 billion; $72 million in multiyear grants for malaria control approved in April 2002. http://www.globalfundatm.org/journalists/	Geneva, Switzerland	Global
Malaria Medicines for Venture (MMV)	1999	Facilitates discovery, development, and commercialization of anti-malarial drugs at affordable prices for areas most affected by malaria; public-private partnership fosters collaborations between scientists and pharmaceutical companies to yield one new product every five years. Total budget US$40 million http://www.malariamedicines.org/	Geneva, Switzerland	Global
Roll Back Malaria Partnership (RBM)	1998	Promotes national governance, assists governments to set goals, and co-ordinates malaria control programs; supports endemic countries in developing national health systems as a major strategy for controlling malaria. Annual budget US$35 million http://www.who.int/inf-fs/en/fact203.html	Geneva, Switzerland	Malaria-endemic regions
Malaria Vaccine Initiative (MVI)	1998	Accelerates clinical development of promising malaria vaccine candidates and field trials of vaccine candidates; co-ordinates efforts with various malaria vaccine programs; identifies gaps in current research and applies resources to advance promising malaria candidates. Annual budget US$ 15 million http://www.malariavaccines.org	Rockville, Maryland	Global
Multilateral Initiative on Malaria (MIM)	1997	Global research and control alliance of organisations and individuals concerned with malaria research and control in Africa, maximises the impact of scientific research on malaria in Africa through promotion of capacity building and facilitation of global collaboration and co-ordination. Annual budget US $2 Million http://mim.Su.se	Stockholm, Sweden	Strengthening research capacity in Africa
African Malaria Network[74] (AMANET)	1996	Regional training and organisation of clinical trials and regional co-operation; improves capacity of African institutions and scientists in conducting malaria research including vaccine trials Annual budget: Estimated US$ 500,000 http://www.amvtn.org/	Dar es Salaam, Tanzania	Africa
MFI Malaria Foundation International (MFI)	1992	Advocacy and enhance communication and maximize exchange of views and expertise among malaria scientists and health workers, and encourage cost-effective use of available resources. http://www.malaria.org	New York, NY	Global

* HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome.

The most striking feature of the 1880–1949 period was the connectedness and balance between malaria research and control. The experiences from areas where malaria has been controlled or eliminated show that a combination of scientific originality, perseverance in research, integrated approaches, and social concern were the keys for success. The elimination of *An. gambiae* from Upper Egypt in 1942 is cited as a prime example of malaria control during the first half of the 20th century where those factors were brought together.[63]

Global eradication was not achieved because of (to date) inability to overcome the complex interaction of scientific technical, administrative, financial, logistic, political, and so-
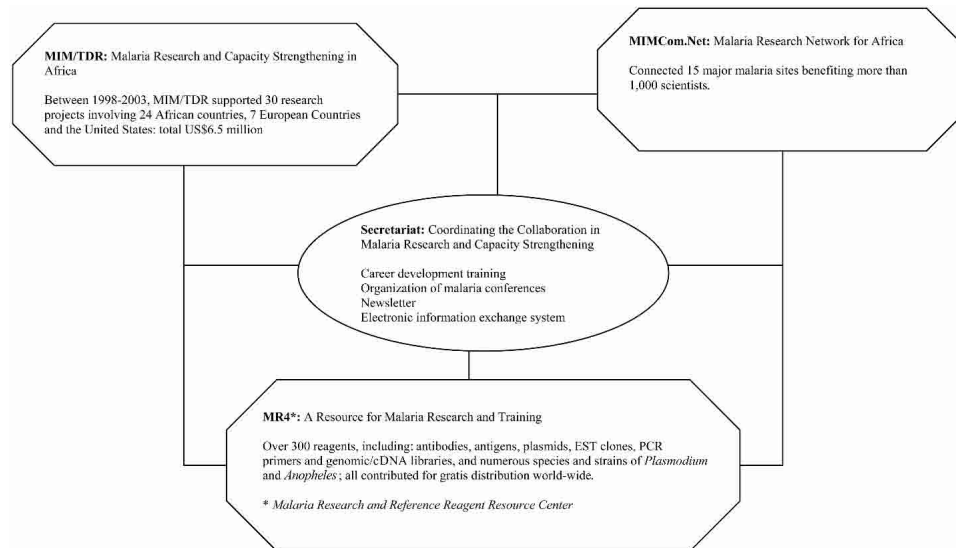
FIGURE 1. Major components of the Multilateral Initiative on Malaria (MIM), 2003. TDR = Special Program in Training and Research in Tropical Diseases; EST = expressed sequence tag; PCR = polymerase chain reaction.

cial challenges. However, in many countries of southern Europe antimalarial measures were remarkably successful, ultimately eliminating the disease. The eradication era afforded substantial experience with new antimalarial tools (e.g., DDT and other insecticides, chloroquine and quinine) and a wealth of research experience that allowed evaluation interventions to be used on a large scale. The experience underscored the importance of national health services in undertaking the exacting operations, the value of international cooperation, standardization of intervention measures, and hard-earned appreciation of the technical and administrative problems blocking successful control and elimination.

The malaria eradication era had some unfortunate consequences. The initial highly encouraging results, largely obtained in temperate or subtropical areas where transmission was unstable, engendered undue optimism for the success of identical antimalarial measures elsewhere. This fostered the view that the total eradication was in sight, such that support for malaria research virtually ceased. Young, bright scientists were discouraged from seeking a career in a discipline that appeared to soon become superfluous. Some have noted wryly that the WHO program failed to eradicate malaria, but it did, effectively, eliminate malariologists. While these limitations became apparent in the 1960s, it took another three decades to modify antimalarial strategies and to rehabilitate long-term control as an intermediate objective. It was becoming understood that elimination of the disease would become feasible only through social and economic evolution, strengthening of health care systems, and the development and effective deployment of new tools. The virtual absence of new tools and methods of control such as a vaccine, has been a major obstacle to reactivating national and international interest, even when the disease has resurged dramatically in areas such as Sri Lanka and India where it had been eliminated during the eradication campaign.

Appreciation of the constraints on the control of malaria led to the establishment of the TDR. Its malaria priorities are improved diagnosis, chemotherapy, immune protection, and clinical epidemiologic research in the field. The TDR pro-

grams have encouraged other funding bodies to resume or increase support for malaria research. As a result, many new findings have been made over the past decade, leading to innovative ways of controlling malaria. Guarded optimism has begun to emerge especially since the recent sequencing of the complete genomes of *P. falciparum* and *An. gambiae.* With the human genome sequence, these new data will allow malaria research to proceed more rapidly.

As the number of multilateral organizations and initiatives continues to grow, so does the need for coordination and communication.[64–71] Closer relationships are developing between research and control through the MIM and the RBM program. This is critical where funding is limited. If major reductions of malaria deaths are to be achieved, it is essential that donors and target populations know the roles and functions of partner organizations, most importantly those of national authorities. This will require partners to contribute to institutional and human capacity development with funding and infrastructure support. This will result in strengthening the cadre of well-trained leaders in research and control who will remain to work on other diseases when malaria is brought under control.

Finally, are multilateral malaria research and control programs the most successful? The answer is yes. The evidence points to substantial progress attained through the new international multilateral collaborations as well as the experience, however painful, from earlier years. Such activities bring substantial additional funds and expertise in to malarious regions that often lack these necessities. Multilateralism underscores the transnational nature of the threat and the need for collaboration to achieve optimal reduction of morbidity and mortality. Examples of other successful multilateral programs are The Global Alliance for Vaccines and Immunization and the Expanded Program on Immunization in reducing the incidence of vaccine preventable diseases, and the Onchocerciasis Control Program in west Africa. These have demonstrated the value of strong leadership, clear goals, good management, frequent widespread communication and transparency, and international collaboration involving the public

TABLE 5
Regional scientific networks created through the multilateral initiative on malaria, 1998–2004

| Research theme | Research institutions | | | | Major achievement |
	East Africa	Central Africa	Southern Africa	West Africa	
Antimalaria drug resistance network	Tanzania, Uganda, Kenya			Ghana, Mali, Nigeria	Using a standard protocol to study systematically host and parasite factors contributing to antimalarial drug resistance. Established a team of African scientists as resource persons to facilitate the network.
Epidemiology and information technology*	Kenya, Tanzania, Uganda	Cameroon	Botswana, Mozambique, Namibia, South Africa, Swaziland, Zambia	Benin, The Gambia, Burkina Faso, Guinea-Bissau, Mali, Senegal	Collated continental data on the epidemiology of malaria. A low-end IT tool with maps (MARA lite) available in CD format.†
Pathogenesis and immunology	Sudan	Cameroon, Gabon		Burkina Faso, Ghana, Nigeria	Training platform for graduate studies in malaria immunology and pathogenesis.
Vector biology and insecticide resistance	Ethiopia, Kenya	Cameroon	South Africa, Swaziland	Benin, Burkina Faso, Ghana, Côte d'Ivoire	Mapping the distribution of insecticide resistance in anopheline vectors in western, eastern, and southern Africa.

* Additional funding available to the MARA network through the South Africa Medical Research Council, the International Development Research Center of Canada, Roll Back Malaria, the Swiss Tropical Institute, the Wellcome Trust, and the World Health Organization.
† IT = information technology; MARA lite = Malaria Research Alliance, essential data only.

and private sectors. There are very few examples of any country acting on its own and achieving a substantial reduction in morbidity and mortality due to malaria.

There are cautionary notes. While eradication of malaria in southern Europe, some parts of Asia, and Brazil are great successes, there are many failures, including the gaps in accountability and lack of long-term strategies for maintaining the program over extended periods. The global momentum gained during the 1950s was almost completely lost during the 1970s. In Africa, projects such as the Pare-Taveta scheme, Garki, and Kisumu were valuable sources of information, but did not lead to scaled-up multilateral research and control programs. Some multilateral programs were fragmented, lacked long-term vision, engendered funding competition, and created an imbalance of both attention and resources among target countries.

To bring together the many groups working on malaria and focusing on Africa, we propose a non-partisan umbrella mechanism to coordinate the network of many alliances and programs now existing at the global and regional levels. This mega-global entity would focus on increasing opportunities to collaborate and fostering mutually beneficial competition in implementing control activities and research protocols, including drug and vaccine trials. This entity would help ensure optimal training and engagement of a critical mass of leader-scientists and increase the number of centers of excellence working on malaria in developing nations. The coordinating center would promote the commitment of lower- and middle-income health ministries and governments to malaria research and control, and serve as a nerve center for information exchange and dialogue. This would raise the overall quality of malaria-related activities and reduce the accountability gap through standardization of approaches and transparency. Achievement of the goal of reducing the malaria burden requires much more than a proliferation of organizations and initiatives.

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